REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 2-13, 18-26, 56, and 57 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Appropriate corrections to the specification as suggested by the examiner have been made.

New claims 56 and 57 find support in the specification at page 37, lines 15-20 (second full paragraph).

Claims 2, 4-13, 17-26, 31 and 55 have been rejected under 35 U.S.C. 112, first paragraph, because the examiner states that the specification, while being enabling for a method for preparing $CD34^+$ cells *in vivo*, involving administering to a donor a composition comprising growth hormone and a composition comprising G-CSF, and isolating $CD34^+$ cells from said donor, is not enabling for a method of preparing populations of "all" possible circulating cells *in vivo*, by administering to a donor a composition comprising growth hormone derivatives or any factor inducing growth hormone release and a composition comprising G-CSF, and isolating said population of circulating cells. This rejection is respectfully traversed.

The specification at pages 19-29 defines what is meant by a derivative of growth hormone and provides not only numerous

representative examples but also guidance as to modifications that can be made. It should be pointed out that the art of growth hormone, and in particular human growth hormone, is well studied in the prior art. Besides the citations of non-patent publications relating to "derivatives" of growth hormone in the specification at pages 20-24, there are many prior art patent publications disclosing functional derivatives of growth hormone. A sampling of U.S. patents relating to functional "derivatives" of human growth hormone includes U.S. Patents 5,534,617; 5,597,709; 5,633,352; 5,688,666; 5,834,598; 5,843,453; 5,849,535; 5,849,700; 5,849,704; and 5,851,992, copies of the first page of which are attached hereto for the examiner's consideration. As these U.S. patents are only cited to show the state of the art and as the examiner can review these U.S. patents online just as easily as copies scanned for image file wrappers (IFW) by the USPTO, only the front pages of the U.S. patents are attached hereto in an effort to reduce the burden of extra scanning on the USPTO. Those of skill in the art would immediately be guided by the present specification to determine whether or not a derivative of growth hormone is a functional derivative for the purposes of the present invention without undue experimentation.

Regarding "a factor that induces growth hormone", those of skill in the field of growth hormones were well aware of growth hormone releasing hormone and functional derivatives

thereof. A representative sampling of prior art U.S. patents on growth hormone releasing hormone functional derivatives thereof includes U.S. Patents 5,137,872; 5,767,085; 5,776,901; 5,792,747; 5,846,936; 5,847,066; 5,612,470; and 5,696,089, copies of the front pages of which are also attached hereto for the examiner's consideration. Furthermore, Appendix A attached hereto provide an extensive listing of the many prior art publications which demonstrate the state of the art and the wealth of publicly available information on factors which induce growth hormone release at the time the present invention was made.

Accordingly, one of skill in the art is fully enabled for the full scope of the present claims. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 2, 4-13, 17-26, and 55 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner states that the specification does not provide a written description for a growth hormone derivative or any factor inducing growth hormone release to be used in the presently claimed method. This rejection is respectfully traversed.

As discussed in the enablement rejection immediately above, the present specification discloses numerous growth hormone derivatives along with reference citations on pages 19-29, thereby providing a representative number of species within

the genus of growth hormone derivatives. Furthermore, attached hereto are copies of the front page of prior art U.S. Patents which disclose and teach derivatives of growth hormone and a growth hormone releasing hormone (factor inducing release of growth hormone) as well as a listing of factors in Appendix A which have been shown to induce growth hormone release in the prior art. Therefore, while the present specification itself provides an adequate written description, this is supplemented by the wealth of knowledge in the prior art about derivatives of growth hormone and a factor inducing the release of growth hormone.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 4-13, 17-26, and 55 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the amendment to the claims to eliminate dependency from non-elected and cancelled claims 1 and 3.

Claims 2, 4-13, 17-26, 31 and 55 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Haas et al. (1995) in view of Murphy et al. (1992). This rejection is respectfully traversed.

Murphy is applied by the examiner for its disclosure that the administration of recombinant growth hormone leads to stimulation of splenic and bone marrow hematopoietic progenitor

cell content. However, there is no teaching or suggestion in Murphy that growth hormone stimulates the mobilization of hematopoietic progenitor cells to the circulation. Instead, there is strong evidence that stem cell/hematopoietic progenitor cell mobilization to the periphery does not automatically happen just because of increased stem/progenitor number in the marrow or spleen, but rather requires specific mechanisms, including the release of proteases. The release of proteases, as well as many other mechanisms, have been implicated in stem and progenitor cell mobilization from bone marrow and spleen and other hematopoietic organs. These proteases are thought to enable the release of stem cells from matrix proteins by degrading these proteins. There is ample evidence, including Aicher, et al., "Essential role of endothelial nitric oxide synthase for mobilization of stem and progenitor cells", *Nat. Med.* 2003 Nov. 9(11): 1370-6, that an increase in bone marrow and spleen stem cell content does not automatically or inherently lead to an increase in circulating cells capable of regenerating hematopoiesis *in vivo*.

Claim 2 as presently amended positively recites the surprising finding that growth hormone enhances the effect of G-CSF to synergistically increase the mobilization of the number of circulating $CD34^+$ cells capable of regenerating hematopoiesis *in*

vivo. This feature is supported by the specification at page 36, second full paragraph, to page 37, second full paragraph.

Furthermore, in Example 7 on page 56 of the specification, it is demonstrated that, following chemotherapy, there is a surprising doubling or tripling in the mobilization of circulating $CD34^+$ cells in the blood stream when growth hormone is administered with G-CSF (cycle 2) versus the control (cycle 1) where G-CSF is administered alone. Similarly, the surprising finding that growth hormone enhances the effect of G-CSF to synergistically increase the mobilization of the number of circulating $CD34^+$ cells capable of regenerating hematopoiesis *in vivo* is also observed after three cycles of treatment (in relabeled Figure 1 and on page 58 of the specification). It is clear from the replacement sheet labeled Figure 1 attached hereto (which is the same as Figure 2 as originally filed except for being relabeled as Figure 1) that growth hormone in combination with G-CSF synergistically increased the number of circulating $CD34^+$ cells considerably over what was achieved with G-CSF alone. Accordingly, the present invention provides surprisingly superior results that could not have been predicted by those of skill in the art. Consequently, Haas and Murphy cannot lead one of ordinary skill in the art to the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully traversed.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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APPENDIX A

Neuropeptides

- Synthetic growth hormone releasing peptides (GHRP) and their non-peptide analogues
- Bowers CY. Growth hormone-releasing peptide (GHRP). Cellular & Molecular Life Sciences. 54(12):1316-29, 1998.
- Ghigo E. Arvat E. Muccioli G. Camanni F. Growth hormone-releasing peptides. European Journal of Endocrinology. 136(5):445-60, 1997
- Korbonits M. Grossman AB. Growth hormone-releasing peptides (GHRP) and its analogues. Novel stimuli to growth hormone release. Trends Endocrinol Metabol 6:43-49, 1995.
- Galanin
- Bauer FE. Ginsberg L. Venetikou M. MacKay DJ. Burrin JM. Bloom SR. Growth hormone release in man induced by galanin, a new hypothalamic peptide. Lancet. 2(8500):192-5, 1986
- Hulting AL. Meister B. Carlsson L. Hilding A. Isaksson O. On the role of the peptide galanin in regulation of growth hormone secretion. Acta Endocrinologica. 125(5):518-25, 1991
- Opioids
- Opiate peptides control growth hormone through a cholinergic mechanism in man.
  Delitala G, Grossman A, Besser GM
  Clin Endocrinol (Oxf) 1983 Apr 18:4 401-5
- Opioids stimulate growth hormone (GH) release in man independently of GH-releasing hormone.
  Delitala G, Tomasi PA, Palermo M, Ross RJ, Grossman A, Besser GM
  J Clin Endocrinol Metab 1989 Aug 69:2 356-8
- Thyrotropin releasing-hormone (TRH): only under certain experimental & pathophysiological conditions (acromegaly, type 1 diabetes, hepatic & renal failure), but not usually in normal unmedicated subjects.
- Effect of glucocorticoids on the paradoxical growth hormone response to thyrotropin-releasing hormone in patients with acromegaly.
  Giustina A, Doga M, Bresciani E, Bussi AR, Chiesa L, Misitano V, Giustina G
  Metabolism 1995 Mar 44:3 379-83
- Growth hormone response to thyrotropin releasing hormone and placebo in a group of insulin dependent diabetic patients.
  Valentini U, Cimino A, Rotondi A, Rocca L, Pelizzari R, Giustina A, Marchetti C, Romanelli G
  J Endocrinol Invest 1989 Oct 12:9 643-6
- Abnormal TSH, PRL and GH response to TSH releasing factor in chronic renal failure.
  Czernichow P, Dauzet MC, Broyer M, Rappaport R
  J Clin Endocrinol Metab 1976 Sep 43:3 630-7
- Scanlon M, Peters J, Foord S, Dieguez C, Hall R. 1983. Clinical application of TRH. In: Griffiths E, Bennet W (eds). Thyrotropin releasing hormone. Raven Press, New York, pp 303-314.
- Neuropeptide Y (NPY): there are isolated reports of a stimulatory (and inhibitory) effect of NPY on GH release in patients with prolactinoma or acromegaly.
- Stimulation by neuropeptide Y of growth hormone secretion in prolactinoma in vivo.
  Watanobe H, Tamura T
  Neuropeptides 1996 Oct 30:5 429-32
- Stimulatory and inhibitory effects of neuropeptide Y on growth hormone secretion in acromegaly in vivo.
  Watanobe H, Tamura T
  Neuropeptides 1997 Feb 31:1 29-34

- Substance P
- Intravenously infused substance P enhances basal and growth hormone (GH) releasing hormone-stimulated GH secretion in normal men.
  Coiro V, Volpi R, Capretti L, Speroni G, Bocchi R, Caffarri G, Colla R, Rossi G, Chiodera P
  Peptides 1992 Jul-Aug 13:4 843-6
- Melatonin: there are reports of a stimulatory effect and of no effect of melatonin on GH release.
- Melatonin stimulates growth hormone secretion through pathways other than the growth hormone-releasing hormone.
  Valcavi R, Zini M, Maestroni GJ, Conti A, Portioli I
  Clin Endocrinol (Oxf) 1993 Aug 39:2 193-9

Neurotransmitters

- Acetylcholine
- Pyridostigmine treatment selectively amplifies the mass of GH secreted per burst without altering GH burst frequency, half-life, basal GH secretion or the orderliness of GH release.
  Friend K, Iranmanesh A, Login IS, Veldhuis JD
  Eur J Endocrinol 1997 Oct 137:4 377-86
- Inhibition of physiological growth hormone secretion by atropine.
  Taylor BJ, Smith PJ, Brook CG
  Clin Endocrinol (Oxf) 1985 Apr 22:4 497-501
- Cholinergic muscarinic receptor blockade with pirenzepine abolishes slow wave sleep-related growth hormone release in normal adult males.
  Peters JR, Evans PJ, Page MD, Hall R, Gibbs JT, Dieguez C, Scanlon MF
  Clin Endocrinol (Oxf) 1986 Aug 25:2 213-7
- Catecholamines, dopaminergic pathway
- Growth hormone (GH) responses to arginine and L-dopa alone and after GHRH pretreatment.
  Page MD, Dieguez C, Valcavi R, Edwards C, Hall R, Scanlon MF
  Clin Endocrinol (Oxf) 1988 May 28:5 551-8
- Growth hormone response to apomorphine, a dopamine receptor agonist, in normal aging and in dementia of the Alzheimer type.
  Lal S, Nair NP, Thavundayil JX, Tawar V, Tesfaye Y, Dastoor D, Gauthier S, Guyda H
  Neurobiol Aging 1989 May-Jun 10:3 227-31

- Catecholamines, α2-adrenergic pathway
- New evidence for growth hormone modulation by the alpha-adrenergic system in man.
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- Evidence that alpha 2-adrenergic pathways play a major role in growth hormone (GH) neuroregulation: alpha 2-adrenergic agonism counteracts the inhibitory effect of muscarinic cholinergic receptor blockade on the GH response to GH-releasing hormone, while alpha 2-adrenergic blockade diminishes the potentiating effect of increased cholinergic tone on such stimulation in normal men.
  Devesa J, Diaz MJ, Tresguerres JA, Arce V, Lima L
  J Clin Endocrinol Metab 1991 Aug 73:2 251-6
- Serotonin
- Role of the serotonin receptor subtype 5-HT1D on basal and stimulated growth hormone secretion.
  Mota A, Bento A, Penalva A, Pombo M, Dieguez C
  J Clin Endocrinol Metab 1995 Jun 80:6 1973-7

- Effect of 5-hydroxytryptophan (5-HTP) on growth hormone and ACTH release in man.
  Imura H, Nakai Y, Yoshimi T
  J Clin Endocrinol Metab 1973 Jan 36:1 204-6

• γ-aminobutyric acid (GABA)

- Effect of acute and repeated administration of gamma aminobutyric acid (GABA) on growth hormone and prolactin secretion in man.
  Cavagnini F, Invitti C, Pinto M, Maraschini C, Di Landro A, Dubini A, Marelli A
  Acta Endocrinol (Copenh) 1980 Feb 93:2 149-54
- Effects of a gamma aminobutyric acid (GABA) derivative, baclofen, on growth hormone and prolactin secretion in man.
  Cavagnini F, Invitti C, Di Landro A, Tenconi L, Maraschini C, Girotti G
  J Clin Endocrinol Metab 1977 Sep 45:3 579-84
- Effect of gamma-aminobutyric acid on growth hormone and prolactin secretion in man: influence of pimozide and domperidone.
  Cavagnini F, Benetti G, Invitti C, Ramella G, Pinto M, Lazza M, Dubini A, Marelli A, Muller EE
  J Clin Endocrinol Metab 1980 Oct 51:4 789-92

• Histamine: the sparse data available seem to indicate that histamine may play a role in stimulating GH secretion.

- Histamine-induced paradoxical GH response to TRH/GnRH in men and women: dependence on gonadal steroid hormones.
  Knigge U, Thuesen B, Dejgaard A, Svenstrup B, Bennett P
  Acta Endocrinol (Copenh) 1990 Mar 122:3 354-60
- Effect of the antihistaminic agents meclastine and dexchlorpheniramine on the response of human growth hormone to arginine infusion and insulin hypoglycemia.
  Pontiroli AE, Viberti G, Vicari A, Pozza G
  J Clin Endocrinol Metab 1976 Sep 43:3 582-6

Metabolic substrates

• Amino acids: arginine, arginine and lysine

- L-arginine is unlikely to exert neuroendocrine effects in humans via the generation of nitric oxide.
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  Eur J Endocrinol 1996 Nov 135:5 543-7
- The arginine provocative test: an aid in the diagnosis of hyposomatotropism.
  Parker ML, Hammond JM, Daughaday WH
  J Clin Endocrinol Metab 1967 Aug 27:8 1129-36
- A study of growth hormone release in man after oral administration of amino acids.
  Isidori A, Lo Monaco A, Cappa M
  Curr Med Res Opin 1981 7:7 475-81
- Cholinergic-muscarinic receptors participate in growth hormone secretion induced by lysine-8-vasopressin in man.
  Coiro V, Volpi R, Muzzetto P, Caiazza A, Petrolini R, Cerri L, Ruberti G, Chiodera P
  Horm Metab Res 1985 Jun 17:6 316-7

Hormones

• Insulin

- A comparison of the effects of insulin and pyrogen as stimuli to growth hormone release in man.

Raiti S, Blizzard RM, Johanson A, Davis WT, Migeon CJ
Johns Hopkins Med J 1968 Mar 122:3 154-9

- Test of growth hormone secretion in adults: poor reproducibility of the insulin tolerance test.
  Hoeck HC, Vestergaard P, Jakobsen PE, Laurberg P
  Eur J Endocrinol 1995 Sep 133:3 305-12

• Gonadal sex hormones

- Estrogen and testosterone, but not a nonaromatizable androgen, direct network integration of the hypothalamo-somatotrope (growth hormone)-insulin-like growth factor I axis in the human: evidence from pubertal pathophysiology and sex-steroid hormone replacement.
  Veldhuis JD, Metzger DL, Martha PM, Mauras N, Kerrigan JR, Keenan B, Rogol AD, Pincus SM
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- Sex steroid regulation of growth hormone secretion and action.
  Ho KK, O_Sullivan AJ, Weissberger AJ, Kelly JJ
  Horm Res 1996 45:1-2 67-73

• Glucocorticoids: They have stimulatory or inhibitory effects on GH release. A stimulatory effect is observed in glucocorticoid-treated adrenal insufficiency and shortly after administration of dexamethasone.

- Growth hormone deficiency, rapidly reversible during glucocorticoid replacement, in a case of adrenocorticotrophin deficiency.
  Giustina A, Candrina R, Romanelli G
  Neth J Med 1988 Dec 33:5-6 291-7
- Reciprocal relationship between the level of circulating cortisol and growth hormone secretion in response to growth hormone-releasing hormone in man: studies in patients with adrenal insufficiency.
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- Role of glucocorticoids in the neuroregulation of growth hormone secretion.
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• Thyroxine (T4)

- Growth and growth hormone. 3. Growth hormone release in children with primary hypothyroidism and thyrotoxicosis.
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• Glucagon

- Participation of cholinergic muscarinic receptors in glucagon- and arginine-mediated growth hormone secretion in man.
  Delitala G, Frulio T, Pacifico A, Maioli M
  J Clin Endocrinol Metab 1982 Dec 55:6 1231-3
- The glucagon infusion test and growth hormone secretion.
  AvRuskin TW, Tang SC, Juan CS
  J Pediatr 1975 Jan 86:1 102-6

• Pituitary adenylate cyclase activating polypeptide (PACAP)

- Pituitary adenylate cyclase activating polypeptide, growth hormone (GH)-releasing peptide and GH-releasing hormone stimulate GH release through distinct pituitary receptors.
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  Endocrinology 1992 Feb 130:2 939-44